

REMARKS

Status of the Claims

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 are in the application.

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 were rejected.

By way of this amendment, claims 169, 171, 172 and 174 have been amended, claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148, 150-168, 170, and 173 have been canceled, and new claims 175-198 have been added.

Upon entry of this amendment, claims 169, 171, 172 and 174-198 will be pending.

Summary of the Amendment

Claim 169 has been amended to set forth the metes and bounds of the claim. As amended, claim 169 refers to a method of treating an individual who has metastatic colorectal cancer or primary or metastatic esophageal or stomach cancer. In addition, claim 169 has been amended to indicate that the guanylyl cyclase C ligand activates guanylyl cyclase C and that radiation or a cytotoxic therapeutic agent is administered following completion of treatment with guanylyl cyclase C ligand that activates guanylyl cyclase C. Support for the amendment is found throughout the specification, particularly in paragraphs [0073], [0137], [0151], [0170], [0171], [0172], [0211] and [0215] of the published application.

Claim 171 has been amended to correct its dependency and to more clearly set forth that the different therapeutic agent administered is a cytotoxic agent. Support for the amendment is found throughout the specification, particularly in paragraphs [0170] and [0171] of the published application.

Claim 172 and 174 have been amended to correct their dependency.

New claims 175-198 refer to specific embodiments of the claimed invention. Support for new claims 175-198 is found throughout the specification and claims as filed.

No new matter has been added.

Claim Rejections under 35 USC § 103

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 have been rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5,879,656 in view of Shilubhai et al. (Cancer res. sep 15, 2000 60:5151-5157) in view of Cohen (Int Radiat Oncol Biol Phys 1987 13:251-8), in further view of US Patent No. 6,251,439, in further view of Queen et al. (Proc Natl Acad sci USA 1989 86:10029-10033) in further view of Riechmann et al. (Nature 332:323-327 1988).

U.S. Patent No. 5,879,656 is asserted to teach the use of anti-GCC antibodies and GCC ligands to treat primary and metastatic colorectal cancer including in combination with other therapeutic agents.

Shilubhai et al. is asserted to teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppresses polyp formation.

Cohen is asserted to teach that a combination of factors much be found to identify the safest procedure for treating cancer.

US Patent No. 6,251,439 is asserted to teach methods of reducing the risk of colorectal adenoma using calcium.

Queen et al. is asserted to teach methods of making humanized antibodies.

Riechmann et al. is asserted to teach recombinant methods to clone and humanize monoclonal antibodies.

It is asserted that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of U.S. Patent No. 5,879,656 and use different doses and timers of infusion of unconjugated GCC ligands and antibodies comprising therapeutic agents because Shilubhai teach anti-cancer activity of uroguanylin and Cohen teaches optimizing factors. Further, it is asserted that it would have been obvious to administer calcium in combination with the treatment methods of U.S. Patent No. 5,879,656 because U.S. Patent No. 6,251,439 teaches calcium reduces the risk of colon cancer .

It is asserted that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of U.S. Patent No. 5,879,656 with the teachings of Queen et al. and Riechmann et al.

Applicants respectfully disagree.

Nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As discloses in the specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teach or suggest the invention as claimed.

Neither U.S. Patent No. 5,879,656 nor Shilubhai disclose that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in Cohen, US Patent No. 6,251,439, Queen or Riechmann make up for this deficiency. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy.

In addition, nothing in the combination of references teaches that Calcium increases the radiation and chemo-sensitivity which results after GCC activation. Applicants have shown that the role of calcium levels in inducing cell cycle arrest by GCC activation .

Moreover, nothing in the combination of U.S. Patent No. 5,879,656, Shilubhai, Cohen, US Patent No. 6,251,439, Queen and Riechmann teach or suggest that activation of GCC leads to an increase in expression of GCC in cells which results in more targets on cell surfaces against which anti-GCC conjugates. The increase in GCC on the cell surface makes the use of anti-GCC moieties that are conjugated to cytotoxic moieties more effective since more conjugated GCC can be delivered to the cells thereby delivering more toxic substances. Accordingly, the methods of the claimed invention in which a conjugated cytotoxic anti-GCC agent is delivered following treatment with ligant that results in GCC activation are more effective than those in which a

conjugated cytotoxic anti-GCC agent is delivered without prior GCC activation. GCC activation results in upregulation of GCC expression which results in more targets for conjugated cytotoxic anti-GCC agent to bind to and deliver their cytotoxic moiety.

Applicants respectfully request that the rejection the claims under 35 USC 103(a) as being unpatentable over U.S. Patent No. 5,879,656 in view of Shilubhai et al. in view of Cohen in further view of US Patent No. 6,251,439, in further view of Queen et al. in further view of Riechmann et al. be withdrawn.

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 145, 147, 148 and 150-174 have been rejected under 35 USC 103(a) as being unpatentable over U.S. Patent No. 6,767,704 in view of Shilubhai et al. (Cancer res. sep 15, 2000 60:5151-5157) in further view of US Patent No. 6,251,439, and in further view of Cohen (Int Radiat Oncol Biol Phys 1987 13:251-8),.

U.S. Patent No. 6,767,704 is asserted to teach the use of anti-GCC antibodies and GCC ligands to treat metastatic colorectal cancer and primary and metastatic esophageal and stomach cancer including in combination with other therapeutic agents.

Shilubhai et al. is asserted to teach that uroguanylin inhibits proliferation and induces apoptosis in colon adenocarcinoma cells and suppresses polyp formation.

US Patent No. 6,251,439 is asserted to teach methods of reducing the risk of colorectal adenoma using calcium.

Cohen is asserted to teach that a combination of factors much be found to identify the safest procedure for treating cancer.

It is asserted that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to modify the teachings of U.S. Patent No. 6,767,704 and use different doses and timers of infusion of unconjugated GCC ligands and antibodies comprising therapeutic agents because Shilubhai teach anti-cancer activity of uroguanylin and Cohen teaches optimizing factors. Further, it is asserted that it would have been obvious to administer calcium in combination with the treatment methods of U.S. Patent No. 6,767,704 because U.S. Patent No. 6,251,439 teaches calcium reduces the risk of colon cancer .

Applicants respectfully disagree.

Nothing in the combination of references discloses that activation of GCC renders cells more susceptible to radiation or cytotoxic agents. As discloses in the specification, GCC activation leads to elevated levels of cGMP which inhibit and slow the cell's progress through the cell cycle. Administering radiation or cytotoxic chemotherapy after activation of GCC has been completed renders the cells more sensitive to radiotherapy or cytotoxic chemotherapy. Nothing in the combined teachings in the art teach or suggest the invention as claimed.

Neither U.S. Patent No. 6,767,704 nor Shilubhai disclose that GCC activation renders cells more vulnerable to radiotherapy or cytotoxic chemotherapy administered after GCC activation. Nothing in Cohen nor US Patent No. 6,251,439 make up for this deficiency. Nothing in the combination of references teaches or suggests that pretreatment with a GCC activating compound will result in a more effective use of cytotoxic chemotherapy or radiation therapy by reducing the therapeutic index of the cytotoxic chemotherapy or radiation therapy.

In addition, nothing in the combination of references teaches that Calcium increases the radiation and chemo-sensitivity which results after GCC activation. Applicants have shown that the role of calcium levels in inducing cell cycle arrest by GCC activation .

Moreover, nothing in the combination of U.S. Patent No. 5,879,656, Shilubhai, Cohen, nor US Patent No. 6,251,439, teach or suggest that activation of GCC leads to an increase in expression of GCC in cells which results in more targets on cell surfaces against which anti-GCC conjugates. The increase in GCC on the cell surface makes the use of anti-GCC moieties that are conjugated to cytotoxic moieties more effective since more conjugated GCC can be delivered to the cells thereby delivering more toxic substances. Accordingly, the methods of the claimed invention in which a conjugated cytotoxic anti-GCC agent is delivered following treatment with ligand that results in GCC activation are more effective than those in which a conjugated cytotoxic anti-GCC agent is delivered without prior GCC activation. GCC activation results in upregulation of GCC expression which results in more targets for conjugated cytotoxic anti-GCC agent to bind to and deliver their cytotoxic moiety.

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Applicants respectfully request that the rejection the claims under 35 USC 103(a) as being unpatentable over U.S. Patent No. 6,767,704 in view of Shilubhai et al. in further view of US Patent No. 6,251,439, in further view of Cohen be withdrawn.

Conclusion

Claims 169, 171, 172 and 174-198 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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